Understanding Genetic Correlations Between Eye Cancer Patients with Cataract- Causing Mutations

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Abstract:

Cataracts are the number one cause of blindness worldwide. Cataracts occur when the lens of the eye becomes cloudy due to the accumulation of damaged crystallin proteins. When undamaged, crystallins allow the lens to maintain transparency, helping with clear vision. While the genetic basis of cataracts is well documented, there is little research on how the expression levels of cataract-causing genes might be modified in other ocular diseases such as in uveal melanoma. This study analyzes potential genetic correlations between uveal melanoma and cataract-causing genes.

We hypothesize that if uveal melanoma alters the lens environment, then patients with uveal melanoma will exhibit significantly different expression levels of crystallin genes associated with cataract formation.

Using 81 uveal melanoma patient cases sourced from The Cancer Genome Atlas (TCGA), we conducted a comparative genomic analysis by focusing on ten genes from the crystallin family and standardizing their expression levels. Expression levels of the crystallin genes *CRYAA, CRYAB, CRYBA1, CRYBA2, CRYBA4, CRYBB1, CRYBB2, CRYBB3, CRYGC,* and *CRYGS* in all TCGA uveal melanoma cases were determined using the gene expression tool. After refining the dataset by removing outliers exceeding 1.5 times the interquartile range, the model achieved a statistically significant p-value. This value was found when testing correlations between uveal melanoma and cataract formation.

These results supported a genetic correlation between uveal melanoma and cataract expression. Moving forward, more detailed analyses can be done for specific cataract genes (such as *CRYBA*) allowing for connections to be made about molecular interactions leading to specific expression levels.

Introduction:

Gene expression affecting ocular development and function can lead to a broad range of disorders, from cataracts to ocular cancers. While these diseases have many differences in causes and severity, both involve variations in genes that regulate protein stability and lens opacity in the eye.

Cataracts are seen in both developed and developing nations with around 19 million cases worldwide annually [1]. Cataracts occur due to the aggregation of damaged crystallin proteins that results in a loss of their normal lens transparency. New discoveries identifying causative markers in proteins such as crystallins, connexins, and aquaporins give insight into the molecular mechanisms of cataract development. There are many variations of crystallins

needed in the lens. Alpha crystallins act as molecular chaperones to prevent denaturation and aggregation of lens proteins maintaining lens transparency. They also prevent oxidative damage and support the structural integrity of the lens. Beta crystallins are structural proteins that contribute to lens refractivity and are essential for focusing light. They are necessary for maintaining the stability of lens fiber cells. Gamma crystallins are crucial for maintaining the refractive index of the lens and give stability to the lens core [2].

The alpha crystallin genes are *CRYAB* and *CRYAA*. The beta crystallin genes are *CRYBB3*, *CRYBB2*, *CRYBB1*, *CRYBA1*, and *CRYBA4*. The gamma crystallin genes are *CRYGS*, *CRYGD*, and *CRYGC*. These specific genes were chosen because they are the most commonly mutated in people who develop cataracts [3]. Some cataracts are acquired throughout a patient's lifetime, while others are present at birth. In this analysis, the focus is on acquired ones because this is the most common pathogenesis.

Cataracts are typically classified by the age at which they are detected, with some influenced by external variables (high blood sugar, UV radiation, oxidative stress) in people over 50 years old [3]. High expression in αA- and αB-crystallins can lead to autosomal recessive cataracts, especially found in three gene families in *CRYAB*. Decreased levels of functional α-crystallin can provide adequate activity to maintain lens transparency throughout childhood but may increase predisposition to environmental associated and age-developed cataracts.

On the other hand, autosomal dominant cataracts reduce the normal functions and equilibrium of the α-crystallin protein. In addition, CRYAB proteins were found to cause discrete cataracts as well. Discrete cataracts is when clouding occurs in one small area as opposed to across the full lens, and is usually present at birth or due to other diseases [4].

Because CRYAA is specific to the lens and CRYAB is expressed in eye muscle cells, CRYAB leads to a higher rate of myopathy. This said, CRYAB levels can also cause autosomal dominant and recessive cataracts without causing myopathy. As opposed to α-crystallins, most changes that occur in βγ-crystallins are due to crystallin instability associated with an environmental stressor causing molecular aggregates that lead to downstream lens damage and cataract formation.

Furthermore, there is also a relative lack of autosomal recessive activities in β-crystallins and γ-crystallins though the reason for this is unclear. The presence of recessive expression, likely due to the lack of proteins in β-crystallins, indicates that β-crystallins have other roles in the body beyond serving as structural building proteins. Degradation of γ and β-crystallin can form a large variety of cataract phenotypes such as nuclear cataracts which are acquired [5].

In addition to cataracts, other optical diseases, such as uveal melanomas, also have genetic factors that lead to vision loss. Most uveal melanomas are not primary cancers, but rather develop as a result of metastasis from a tumor originating in another region of the body. For example, they can spread from a tumor in another site through the bloodstream or lymphatic system [6]. Breast and lung cancers are the cancers that most commonly metastasize to the eye, due to their high rate of incidence compared to other cancers. Other cancers that can metastasize to the eye include colon, prostate, and skin cancers like melanoma [7].

All types of uveal melanomas are rare, but some of the common ones include intraocular melanomas, retinoblastomas, and intraocular lymphoma.The most common uveal melanoma, intraocular melanoma, arises from melanocytes and generally develops in the uvea. Following intraocular melanoma, retinoblastoma represents another prominent type of uveal melanoma, mainly affecting children [8]. Furthermore, intraocular lymphoma emerges from lymphocytes and is most common in older adults with reduced immune function.

Researchers have identified some risk factors for uveal melanoma, such as age, fair skin color, light eyes, and inherited conditions [9]. Genetic predisposition to uveal melanoma involves disabling tumor suppressor genes, notably *BAP1* for uveal melanoma. *BAP1* is mutated in 47% of uveal melanoma cases [10,11]. Mutations in these genes can cause cells to grow unchecked, increasing risks of developing tumors [12]. Deactivation of the *BAP1* gene is linked to higher risk of developing eye and skin melanomas, mesothelioma, and renal cell cancer [13].

Beyond BAP1, there have been more factors commonly considered in hereditary uveal melanoma, such as PALB2 and MBD4 [14]. PALB2 is intended to suppress tumors as it is responsible for repairing damaged DNA [15]. *MBD4*, a gene linked to fixing DNA pairing mismatches, was also found to influence the onset of uveal melanoma[16,17].

While mutations in *BAP1* are strongly associated with uveal melanoma, hereditary uveal melanoma is not caused by a single gene and often correlates with rates of other cancers [18]. Understanding the molecular functions of both cataracts and ocular cancers can provide key insight for treatment and targeted therapies for these conditions.

The goal of our study was to determine if there is a genetic link between uveal melanoma and cataract causing genes. Here, we hypothesize that if uveal melanoma alters the lens environment, then patients with uveal melanoma will exhibit significantly different expression levels of crystallin genes associated with cataract formation. For this study, we focused on uveal melanoma because it is the most common eye cancer.

Materials and Methods:

Expression Data

The primary dataset for this study was selected from the The Cancer Genome Atlas (TCGA) via the Genomic Data Commons (GDC) portal [19]. To look for the commonalities between cataracts and uveal melanoma, a cohort of 81 patient cases diagnosed with uveal melanoma was identified. In addition to uveal melanoma, these patients were also chosen because they had gene expression data available for expression levels of proteins commonly associated with cataracts, otherwise known as crystallins, in the TCGA database. Specifically, ten candidate genes associated with non-syndromic congenital cataracts were selected for analysis: *CRYAA, CRYAB, CRYBA1, CRYBA2, CRYBA4, CRYBB1, CRYBB2, CRYBB3, CRYGC,* and *CRYGS* (*Table 1)*.

	CRYGS	CRYBB3	CRYBB2	CRYBB1	CRYBA1	CRYBA4	CRYAB	CRYGD	CRYAA	CRYGC
N	81	81	81	81	81	81	81	81	81	81
Missing	0	0	0	0	0	0	0	0	0	0
Mean	−2.47e−11	−4.94e−11	−1.11e−18	1.23e−11	−2.35e−10	−1.11e−10	1.13e−17	−9.88e−11	−2.84e−10	−2.84e−10
Median	−0.254	−0.163	−0.167	−0.135	−0.126	−0.117	−0.265	−0.172	−0.260	−0.235
Standard deviation	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01
Minimum	−0.514	−0.405	−0.175	−0.239	−0.126	−0.127	−1.33	−0.172	−0.260	−0.235
Maximum	7.31	8.18	8.65	8.89	8.94	8.94	3.95	8.66	7.08	6.87

Table 1. Summary of expression level data of 10 candidate genes associated with cataract formation.

Comparative Genomic Analysis

To ensure comparability across patient samples, gene expression values were standardized to a mean of 0 and a variance of 1.01. This facilitated accurate comparative genomic analysis. A heat map visualization was generated to identify initial patterns of up-regulation and down-regulation across the patient cohort.

CRYAB	CRYGD	CRYAA	CRYGC
0.075796742	0.19363332	-0.206816091	-0.235348216
2.570757431	8.657991612	-0.260088293	-0.235348216
-0.386880668	-0.011733184	4.07571295	-0.235348216
-0.506444284	1.73286389	7.075442195	1.275185583
1.721683396	-0.172454797	-0.244636768	-0.235348216
-0.78779245	-0.172454797	-0.220586696	-0.235348216
0.020243926	-0.172454797	-0.260088293	1.396207578
-0.875266472	-0.172454797	-0.063097517	1.234844917
-0.683338143	-0.172454797	1.514380308	-0.235348216
-0.001844126	0.786078874	1.220478087	-0.235348216
0.244730763	-0.057631267	0.608688224	-0.235348216
0.737661871	-0.172454797	-0.260088293	-0.235348216
0.405508611	-0.172454797	-0.260088293	-0.235348216
0.561413499	-0.172454797	-0.260088293	-0.235348216
0.493349577	-0.172454797	-0.245412577	-0.235348216
1.290319359	-0.102902754	-0.250002779	-0.235348216
0.657601596	-0.172454797	-0.214315575	-0.235348216
0.693071811	-0.172454797	-0.260088293	-0.235348216
0.815156685	-0.172454797	-0.260088293	-0.235348216
0.89588221	0.062518321	-0.260088293	-0.235348216
1.091844949	-0.172454797	-0.260088293	-0.235348216
1.008540751	-0.172454797	-0.260088293	-0.235348216
1.152030654	-0.172454797	-0.260088293	-0.235348216
-0.876712971	-0.172454797	0.415188588	-0.235348216
-1.327244232	-0.172454797	-0.260088293	-0.235348216
-1.125059441	-0.172454797	-0.260088293	-0.235348216
-1.181472906	-0.172454797	-0.260088293	-0.235348216
-0.852259301	-0.172454797	-0.260088293	-0.235348216
-0.889945455	-0.172454797	-0.247416749	-0.235348216
0.463219832	-0.172454797	-0.260088293	-0.235348216

Table 2. Heatmap visualization of some cases for genes: *CRYAB, CRYGD,CRYAA, CRYGC*

Next, a comparative genomic analysis was performed to identify markers common to both uveal melanoma and cataract mutation pathways. This overlap analysis filtered genes that exhibited the highest rates of deviation in expression within the group data. Statistical significance was assessed using a one-way ANOVA (Analysis of Variance) done by Jamovi and Gemini statistical software. The initial test yielded a p-value of 1.0, masking any potential significance of the analysis.

Outlier Removal

To address this, an outlier refinement protocol was implemented. Data points greater than 1.5 times the interquartile range, specifically extreme positive outliers, were excluded to isolate primary data correlations (Table 2).This refinement was justified as these isolated, extreme spikes were attributed to an overexpression of genes in one patient which did not accurately depict the overall analysis. If a gene is truly relevant to a disease pathway, one would expect to see a general trend across groups. Retaining these points would have inflated the variance

within groups and hidden the broader, statistically made consensus pathways applicable to both conditions. Following this refinement, a second ANOVA test was performed to evaluate the difference in mean expression levels across the gene groups.

Gene	Total Samples	Outliers Removed	Reason/Boundaries
CRYGS	81	3	High extreme values
CRYBB3	81	6	High extreme values
CRYBB2	81	9	Values significantly outside the tight cluster
CRYBB1	81	5	High extreme values
CRYBA1	81	4	High extreme values
CRYBA4	81	4	High extreme values
CRYAB	81	5	Both high and low extreme values
CRYGD	81	14	Very narrow distribution; many points considered distant
CRYAA	81	16	Very narrow distribution; high extreme values
CRYGC	81	6	High extreme values

Table 3. Summary of outliers removed for each gene and the corresponding reason for removal.

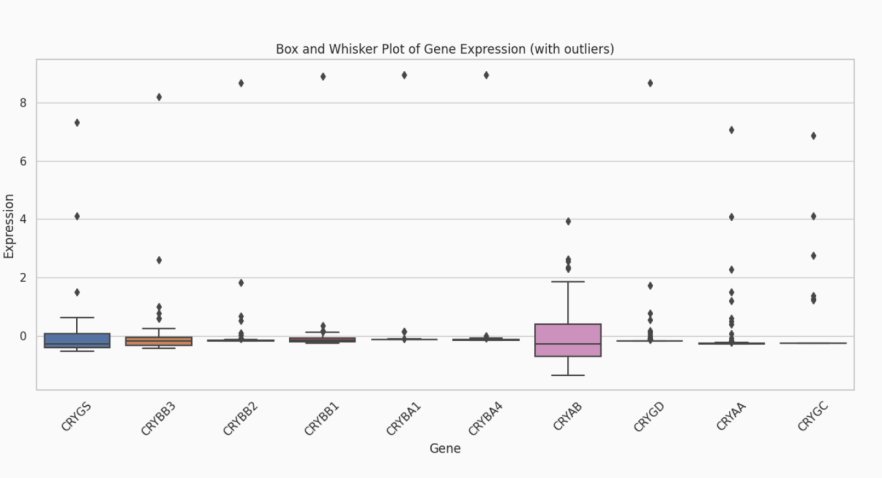
Pairwise Comparison Between Gene Families

To determine specific pairwise differences between gene families, a Tukey's Honestly Significant Difference (HSD) post-hoc test was applied. This allowed for an examination of the data, specifically comparing the alpha-crystallin and beta-crystallin families.

Results

We first began analyzing the data by comparing the gene expression between the 10 genes included in the analysis (Figure 1). The gene expression numbers had already been standardized as demonstrated by the fact that the mean for each gene was approximately 0, and the variance was around 1.01. The median expression levels across most genes were tightly grouped between -0.11 and -0.26 after the removal of outliers. CRYAB showed the largest interquartile range, suggesting broader variations compared to the other genes.

(a)



(b)

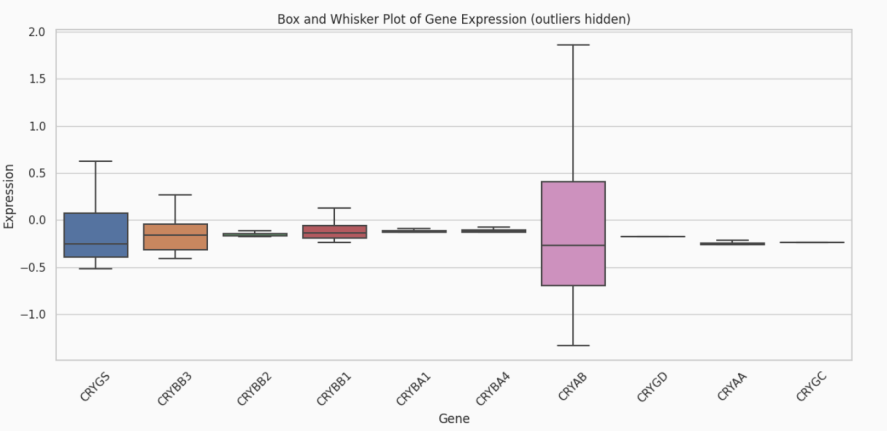


Figure 1. Comparison of gene expression between different genes (a) with and (b) without outliers plotted.

All genes showed extreme positive outliers up to 8.9 fragments per kilobase of transcript per million mapped reads (FPKM), suggesting specific cases had some cataract genes that were highly overexpressed. FPKM is a standardized unit of measurement used in RNA sequencing to quantify the expression levels of genes or transcripts.

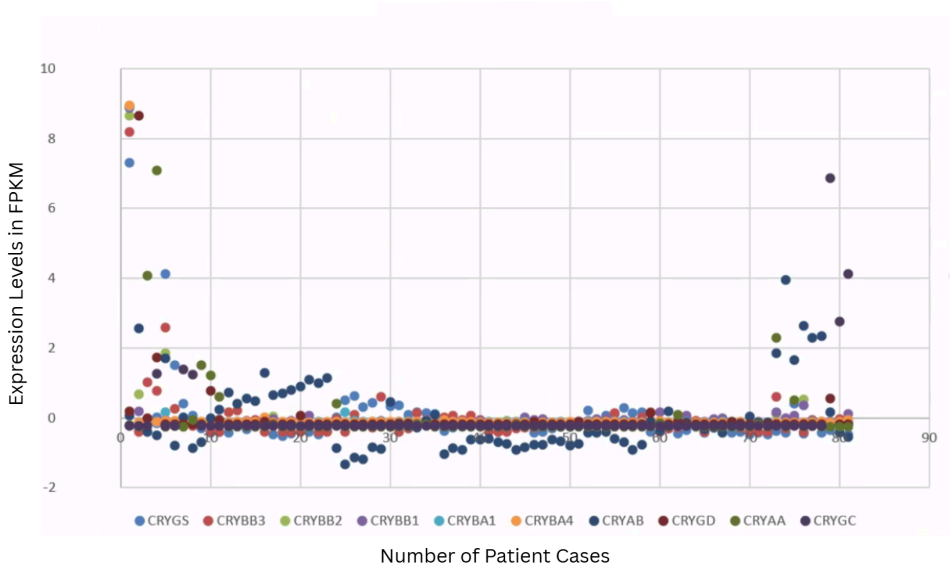


Figure 2. Visual of expression levels in each of the 81 patient cases

Two separate one-way ANOVA (Analysis of Variance) tests were conducted to determine if the mean expression levels differed significantly between genes. The first ANOVA included all expression levels for all the genes before exclusion of outliers. This test resulted in a p-value of 1.0 which was due to the high level outliers covering any underlying differences in the means, making the groups statistically identical. In the second ANOVA test where outliers were excluded (where outliers were defined as values outside 1.5 times the IQR), the p-value was 0.0118, demonstrating that when the extreme cases are removed there is a significant difference in the expression levels of these genes. Out of the 810 total patient cases, 72 (8.89%) were removed due to high extreme values, narrow distribution, and many distant points. CRYAA had a significantly lower average baseline expression overall especially when compared to CRYBA4 (p-value of 0.0355) and CRYBA1 (p-value of 0.0486). To distinguish which genes were causing the significance found after the second, refined ANOVA, a Tukey HSD (Honestly Significant Difference) test was done (Figure 3).

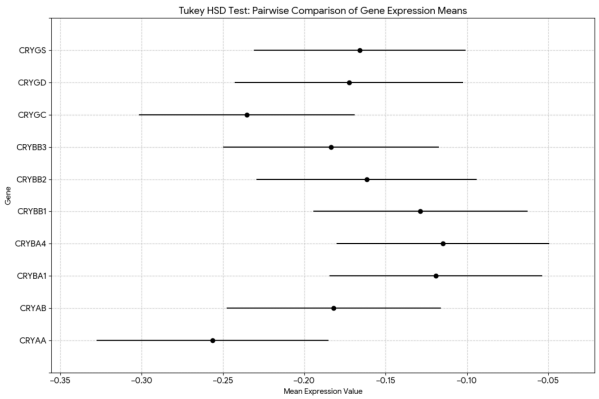


Figure 3. Pairwise comparison of mean gene expression between the genes using Tukey HSD tests.

The most prominent result from the Tukey HSD was that the alpha-crystallin a chain (*CRYAA*) showed a significantly lower mean expression level compared to the CRYBA family. While both are crystallin proteins, *CRYAA* was identified as a statistical outlier in terms of its expression behavior within the uveal cancer patient cohort. The test confirmed that there were no significant differences between the expression levels of the beta-crystallin genes (*CRYBB1, CRYBB2,* and *CRYBB3*). These genes are expressed with a high degree of uniformity, suggesting they likely respond to the same regulatory signals or pathways in the presence of uveal melanoma.

Analysis associated with this phase showed that CRYAB exhibited the largest interquartile range. This means that the CRYAB expression is more diverse, with more spread apart data points instead of tight clustering. The Tukey HSD results provided the data supporting the overall p-value of 0.0118, thus concluding that the statistical significance found in the ANOVA was not just a general trend, but was driven by specific disparities between gene groups. Most notably this trend was driven by differences between the alpha and beta groups).

Discussion

Crystallins are the primary structural proteins of the eye lens, and alterations in their expression are often linked to cataract formation. This study examined the expression profiles of ten crystallin-related genes (*CRYGS, CRYBB3, CRYBB2, CRYBB1, CRYBA1, CRYBA4, CRYAB, CRYGD, CRYAA,* and *CRYGC*) across 81 clinical cases in patients with uveal melanoma, specifically uveal melanoma.

This study revealed that while most crystallin genes maintain a similar baseline expression level across the uveal cancer patients, *CRYAA* (Alpha-crystallin A chain) stands out as having a significantly lower mean expression level than members of the *CRYBA* (Beta-crystallin A) family.

One possible explanation for why CRYAA expression is lower than beta-crystallins such as CRYBA, is due to oxidative stress causing altered gene expression regulation or hypermethylation. In age-related cataracts, the promoter area of the CRYAA gene undergoes hypermethylation, a process characterized by adding excess methyl groups to DNA. This acts as a ‘silencing’ mechanism and often affects tumor suppressing genes [20]. As a result, the transcription factors are unable to bind to the promoter, reducing the expression of CRYAA [21].

The presence of extreme outliers in every gene category suggests that cataract formation in certain individuals may be driven by massive overexpression of specific crystallins, which differs from the usual case profile. No significant differences were found between the various beta-crystallin genes (*CRYBB1, CRYBB2, CRYBB3*), suggesting they are regulated or expressed with a high degree of uniformity in this dataset. This suggests that in this specific study population, the *CRYAA* gene shows a distinct expression pattern compared to the *CRYBA* family. This also suggests that in uveal cancer patients, there tends to be a higher rate of mutation in *CRYAA* genes than the other crystallin genes.

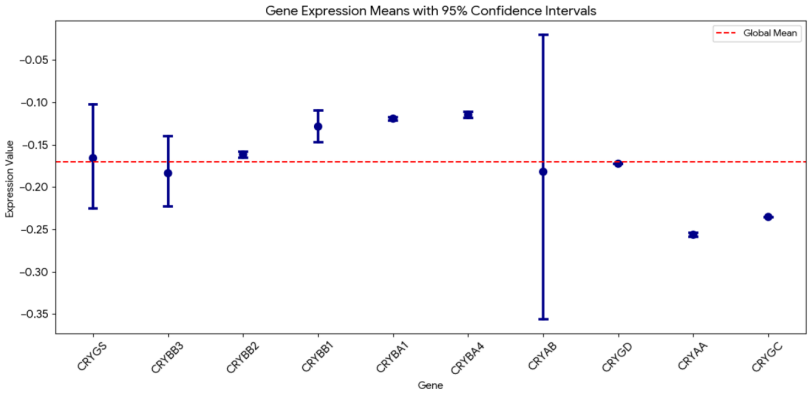


Figure 4. Gene expression means with 95% confidence intervals

While this study has many strengths, there are also some limitations that should be addressed in future work. For example, although the removal of the extreme outliers helped remove noise throughout the data, it may be excluding relevant information. In addition, the use of a one-way ANOVA test assumes normal distribution and homogeneity across groups, and may oversimplify more complex interactions between uveal melanoma and cataracts. Next, these comparisons relied on cohort data from a public repository, TCGA. This could cause selection bias and confounding variables, such as the patient's age and cancer development, which could not be fully standardized. Finally, this analysis was purely done in software and is considered a dry lab study. To validate the findings of the study, *in vitro* or *in vivo* functional testing is required to confirm the behavior of these genes.

To further explore the relationships between uveal melanoma in cataracts, more investigative analyses could be done. Given the lower expression of CRYAA in uveal melanoma patients, future studies could research the effects of the environment on the gene suppression. Since a crystallin is a molecular chaperone, when it decreases it could show why uveal melanoma patients are more prone to lens degeneration. A future study could track the rate of cataract formation in uveal melanomas for the outlier patients in the dataset. This would show any clear patterns or predictions for high expression and progression of disease. Another method would be to find the cause of the similar expression of the CRYBB family. The knowledge of this pathway or system would allow for more stabilized crystallin expression which could protect the lens cells structurally.

This study may provide a foundation for future inquiry aimed at mapping interactions in the eye. Understanding this will be essential for finding new screening methods or interventions that help prevent diseases in the eye.

Conclusion

This study undertook a comprehensive comparative genomic analysis to map the intersection between uveal melanoma and cataract causative pathways, utilizing filtered data from shared gene cohorts. By using a statistical process via a one-way ANOVA test and implementing a targeted outlier refinement protocol to remove outliers, this analysis was able to determine correlations between uveal melanoma and cataracts.

This project reports a genetic correlation between cataract expression and uveal melanoma mutations. While crystallins are largely known as the protective and structural parts of the lens, this analysis shows that their behavior is changed when uveal melanoma genes are present.

By identifying that the CRYAA genes exhibit a significantly lower mean expression than CRYBA, the findings suggest that certain crystallin genes are more altered by the crossover with uveal melanoma. Additionally, the presence of extreme outliers across all ten genes show that while there is a found baselines for most patients, a certain group of individuals experienced a massive overexpression.

Collectively, these insights provide a foundational framework for understanding ocular diseases and highlight the importance of genomic analyses for disease pathways.

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